REMARKS

Applicants request respectfully that the allowability of the claims be reconsidered in view of the above amendments and the following remarks.

Status of the Claims

Claims 1, 7, 11, 14, 15, and 20 to 27 have been amended. No claims have been added or cancelled with the present amendment. The claims pending presently are Claims 1, 7, 11, 14, 15, and 18 to 32.

Discussion of the Amendments

Claim 1 has been amended to clarify that the DNA is sequestered within the complex of the final colloid. In addition, for the sake of consistency, the singular form of complex is used in the claim. Claims 1, 7, 11, 14, 15, and 20 to 27 have been amended to clarify that the polymers referred to therein are cationic. Support for these amendments is found in the application at page 3, lines 21 to 27, of the application. In addition to the above, a typographical error was correct in Claims 20 and 24.

No new matter has been added.

Discussion of the Invention

Applicants' invention is that of a process for making a stable colloid that comprises a complex of DNA and lipids and polymers. The lipids or polymers surround the DNA and sequester it. It is understood in the art that a colloid is a substance that comprises a suspension of particles. In the present case, the particles

are the complexes. Accordingly, the colloid may comprise more than one DNA-containing complex. Support for a colloid comprising more than one complex is found in the application at the bottom of the third full paragraph of page 9 of the application.

In the art, it is known to form complexes of DNA and lipids and polymers in which the lipids or polymers surround the DNA and sequester it. Because DNA is anionic, the most efficient way of forming such a complex is to use cationic lipids or cationic polymers. The cationic lipids or cationic polymers electrostatically interact with the DNA and form an envelope around it. An undesired feature of such a complex, however, is that the exterior (surface potential) of the complex is also cationic. In *in vivo* use, such a cationic exterior causes anionic proteins to be attracted to the complex and cause it to be rapidly opsonized within the cell.

Given the above, it is desired to modify the complex such that the interior of the lipid/polymer envelope around the DNA remains cationic (thus continuing to electrostatically interact with the anionic DNA) while the exterior of the envelope is made either neutral or anionic. Various methods are known in the art for accomplishing this. Such methods are described in Monahan et al. and in Trubetskoy et al. (both cited by the Examiner). In Monahan et al., N-hydroxysuccinimide ester or citraconic anhydride is used in the creation of anionic polymers which are then used to form a second anionic envelope around the initial cationic envelope (the anionic polymers interact electrostatically with the cationic polymers of the initial envelope). Thus a two envelope complex is formed. Trubetskoy et al. also describes generally the formation of a second anionic envelope around the initial cationic envelope. Another method is described in Semple et al. In this method, the cationic lipid/polymer envelope is made using lipids/polymers which become anionic or neutral depending upon the pH of the surrounding environment. If the pH of the surrounding

environment is high, hydrogen atoms on the lipids/polymers on the exterior surface of the envelope are released, thus converting the lipids/polymers on the exterior of the envelope into anionic or neutral lipids/polymers. The lipids/polymers on the interior are not exposed to the surrounding environment and thus remain cationic and thus can continue to associate with the anionic DNA sequestered in the complex.

Applicants' development is novel and non-obvious in that, unlike Monahan et al. and Trubetskoy et al., it does not require the formation of a second anionic envelope around the cationic envelope. Rather, like Semple et al., applicants modify the exterior surface lipids/polymers of the cationic lipid/polymer-DNA complex so that the surface lipids/polymers become netural or anionic. Unlike Semple et al., however, applicants' method does not require a change in the pH of the surrounding environment. Rather, N-hydroxysuccinimide acetate (NHS acetate) or citraconic anhydride (CCA) is used to react with the cationic lipids/polymers on the exterior surface of the cationic envelope, thus converting the exterior lipids/polymers into anionic or neutral form. As the above reactions result in the addition of a chemical moiety to the lipids/polymers and not the release of a hydrogen atom (as in Semple et al.) and as a further anionic envelope is not added (as in Monahan et al. and Trubetskoy et al.), not only is applicants' method novel and non-obvious over the prior art but applicants' colloid is structurally different from the colloids of the prior art and novel and non-obvious thereover as well.

Traversal of the Examiner's
Section 102(e) Rejection of Claims 18 to 23 and 30 Based on Monahan et al.

The Examiner has rejected Claims 18 to 23 and 30 as being anticipated under Section 102(e) by Monahan et al. The Examiner stated that, absent evidence to the contrary, applicants' colloid can not be distinguished from that described in Monahan et al.

In applicants' previous Reply, dated January 23, 2006, applicants argued that the colloid as defined by the claims distinguishes over that described in Monahan et al. in that the colloid of the present claims comprises a DNA-containing complex (DNA sequestered within a layer of cationic lipids or cationic polymers) which is not enveloped by an further layer of anionic or neutral lipids or polymers. By contrast, the colloid of Monahan et al. contains a DNA-containing complex (DNA sequestered within a layer of cationic polymers) which is enveloped by an outer layer of anionic polymers (see column 23, lines 56 to 59, of Monahan et al.). The colloid of applicants' invention is, therefore, significantly different from that of Monahan et al. in that the outer envelope of anionic polymers is not present in the complex of the presently-claimed colloid.

In the Reply, the Examiner does not address the above argument. Instead, the Examiner stated that the argument related to the complex only and not to the claimed colloid. The Examiner then alleged that the colloid of the present invention, being a "stable colloid", is the same as that of Monahan et al. The Examiner failed to consider, however, that the colloid comprises the complex and, inasmuch as applicants' complex differs from that of Monahan et al., the colloid which comprises it must necessarily be different from the corresponding colloid of Monahan et al. as well.

The Examiner then appears to allege that applicants argued that the product differs from that of the prior art because the process used to make it is different from that of Monahan et al. While applicants agree that the Examiner is correct in the statement that the patentability of product-by-process claims is based on the product itself regardless of how the process is made, applicants submit respectfully that the Examiner is incorrect in the belief that applicants argued that the claimed colloid distinguishes over the colloid of Monahan et al. only in the process by which it was

made. As stated above, and as argued in applicants' previous Reply, the colloid itself is substantially different from that of Monahan et al.

In view of the above, applicants request respectfully that the Examiner withdraw the anticipatory rejection of Claims 18 to 23 and 30.

Traversal of the Examiner's Section 103(a) Rejection
Based on Semple et al., Monahan et al., and Trubetskoy et al.

The Examiner has rejected Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 as being rendered obvious under Section 103(a) by:

(A) U.S. Patent No. 6,287,591 to Semple et al., which discloses the use of a buffer to change the surface potential of a DNA-cationic lipid complex to render it neutral; in view of

(B) Monahan et al., which discloses the use of CCA to react with a cationic polymer to render it anionic and the use of the resulting anionic polymer in the formation of an anionic envelope around a DNA-cationic polymer complex (In contrast to the Examiner's understanding, Monahan et al. does not disclose the use of NHS ester to react with a cationic polymer to render it anionic. Rather NHS ester is used to react with two anionic moieties to form an anionic polymer. Further, the resulting anionic polymer is also used to form an envelope around the DNA-cationic polymer complex.); and

(C) U.S. Application Publication No. 2003/0026841 to Trubetskoy et al., which claims priority to a provisional application filed on December 31, 1999 and discloses the use of anionic compounds in the formation of an

anionic envelope around a DNA-cationic polymer complex and states further that the addition of certain anionic compounds may destabilize the complex.

The Examiner argues that one skilled in the art would have been motivated by Trubetskoy et al. to modify the DNA-cationic lipid complexes of Semple et al. by adding anionic compounds and been further motivated by Monahan et al. to create such anionic compounds by reacting cationic polymers with CCA or NHS ester (as stated in the previous Reply and repeated above, however, the Examiner is incorrect in the belief that Monahan et al. discloses the use of NHS ester to react with cationic polymers).

In applicants' Reply dated January 23, 2006, it was argued that the Examiner has failed to establish a *prima facie* case of obviousness because it was not shown that one skilled in the art would have, based on the prior art, had any expectation that applicants' invention would work for its intended purpose. According to the MPEP (see Section 2143 thereof), in addition to the requirements that the combined disclosures teach or suggest each element of the claims and that there must be a suggestion or motivation to combine the teachings of the cited art, the Examiner must also show that one skilled in the art would have had a reasonable expectation that applicants' invention would work for its intended purpose in order to establish a *prima facie* case of obviousness. Applicants submit that the Examiner has failed to meet this requirement for establishing a *prima facie* case of obviousness. While this deficiency was pointed out in our Reply of January 23, 2006, the Examiner did not address this in the April 14, 2006 Action. For the sake of completeness, the argument is reiterated below.

The rejected claims are directed to: (A) a method for making a stable colloid for gene transfer, the stable colloid comprising a complex which comprises DNA sequestered therein and which has a neutral or net anionic surface potential, the process comprising modifying a precursor colloid comprising a complex which has a cationic surface potential and which comprises DNA and cationic lipids or cationic polymers, the DNA being sequestered within said complex, by reacting a NHS acetate or CCA with the cationic lipids or cationic polymers present in said complex to reduce, remove or reverse the cationic surface potential; (B) a stable colloid made using such a process; and (C) a method for using such a colloid.

Prior to applicants' invention, one skilled in the art would not have had any expectancy that the modification of a precursor colloid by reacting CCA or NHS acetate with the cationic lipids/polymers of a DNA-cationic lipid/polymer complex therein would result in a stable complex. Such a reaction effectively converts some of the cationic lipids/polymers in the complex into neutral or anionic lipids/polymers. As stated in Trubetskoy et al. (see paragraph [0043] thereof), which was one of the references cited by the Examiner, the result of the addition of anionic compounds to a DNA-cationic lipid/polymer complex is unpredictable as the addition of certain anionic compounds may lead to destabilization of the complex. This is because the DNA-cationic lipid/polymer complex is held together by the electrostatic interaction of DNA, which is negatively charged, with the cationic lipids/polymers. The addition of certain anionic compounds may disrupt this. For example, depending upon the type of anionic compound used, the cationic lipids/polymers may interact solely with the anionic compound and no longer complex with the DNA. Thus the stability of applicants' complex can not be predicted simply because DNA-cationic lipid/polymer complexes to which other anionic compounds have been added are stable. Accordingly, without a prior teaching or suggestion that the reaction of CCA or NHS acetate with the cationic lipids/polymers in a DNA-containing complex would result in

a stable complex, one skilled in the art would not have had any expectancy that applicants' invention would produce stable complexes.

While Monahan et al. does teach the use of CCA (but not NHS acetate) to modify a cationic polymer and render it anionic, it does not teach or suggest such modification with respect to a cationic polymer which is already present in a DNA-containing complex. Rather it teaches the creation of such an anionic polymer separate and apart from the DNA-containing complex and the subsequent addition of the resulting anionic polymers to form an anionic envelope around the DNA-cationic polymer complex. This is entirely different from what occurs in applicants' process wherein CCA or NHS acetate is reacted with cationic lipids/polymers that are part of the DNA-containing complex to render them neutral or anionic. Applicants' process not only results in the effective addition of neutral or anionic lipids/polymers to the complex (by way of conversion of cationic polymers/lipids therein) but also in a net loss of cationic lipids/polymers from the complex. One of skill in the art would, therefore, expect that there may be an effect on the stability of the complex and that this effect would be different from that achieved in Monahan et al. The loss of cationic polymers may lead to destabilization of the DNA-cationic polymer complex and the effect thereof would be compounded by the effective addition of neutral and anionic polymers to the complex. By contrast, in Monahan et al., the complexes do not loose cationic polymers.

Given the above, Semple et al., Monahan et al., and Trubetskoy et al. do not render applicants' claims obvious and the Examiner's Section 103 rejection of Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 based thereon should be withdrawn.

Discussion of the Examiner's Section 112 Rejection

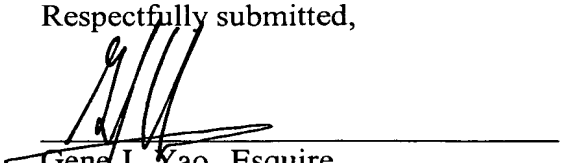
The Examiner rejected Claims 1, 7, 11, 14, 15, and 18 to 32 under the written description requirement of Section 112, first paragraph. According to the Examiner, the amendments presented in the Reply, dated January 23, 2006, added new matter since, according to the Examiner, the claims no longer required that the DNA be sequestered within the complex and that the claims implied that the process defined therein created a colloid comprising multiple complexes from a colloid containing one complex.

In accordance with the Examiner's recommendations, made during an August 10, 2006 telephone conference, independent Claim 1, from which the remaining claims depend, was amended to clarify that the DNA referenced therein is sequestered within the complex. In addition, to be consistent, the singular form of complex is used in the claim. However, applicants submit that it should be understood that the colloid, as defined by the claims, may comprise more than one DNA-containing complex. That this is the case is demonstrated in the application at the bottom of the third full paragraph of page 9 of the application.

Conclusion

In view of the above amendment and remarks, an early and favorable Action is requested respectfully.

Respectfully submitted,



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